SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 30 November 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Paxene concentrated solution for infusion contains the active drug substance paclitaxel. It is a naturally occurring product derived from the Yew tree. Paclitaxel is a cytotoxic anti-cancer drug. The indication for Paxene is the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy. The recommended dose is 100 mg/m^2 administered as a 3-hour intravenous infusion every 14 days. Courses of therapy may be delayed or the dosage reduced depending on the observed toxicity.

A disseminated, fulminant form of KS occurs in individuals infected with the human immunodeficiency virus (HIV). Approximately 20% of patients with AIDS have AIDS-related Kaposi's sarcoma (AIDS-KS). AIDS-KS is characterised by multifocal, widespread lesions of the skin, mucosal surfaces, lymph nodes and visceral organs, including the liver, spleen, gastro-intestinal (GI) tract and lungs. Where KS is confined to the skin, AIDS patients are often healthy and free of systemic symptoms and therapy may not be required. However, the psychosocial burden associated with facial and other dermal involvement may be profound. Although most patients initially present with skin disease, KS involvement of the lymph nodes or the GI tract may occasionally precede the appearance of cutaneous lesions. Eventually, almost all patients with epidemic KS develop disseminated disease. Life-threatening lesions most commonly involve the GI tract and lungs. However, most patients with AIDS-KS die of opportunistic infections rather than the disease itself.

Management of AIDS-KS is generally directed at palliation of disease-related symptoms as no treatment has been unequivocally proven to impact survival. Local therapy (radiation or laser therapy, intralesional administration of cytotoxic agents) may result in the disappearance or reduction in size of lesions and thereby alleviate symptoms. However, advanced AIDS-KS usually requires systemic therapy.

2. Chemical, pharmaceutical and biological aspects

Composition and product development

Paxene is a concentrated solution for infusion containing either 30 mg/5 ml or 150 mg/25 ml of paclitaxel, in a co-solvent system consisting of a 50:50 mixture of ethanol and polyoxyl castor oil, stabilised by 2 mg/ml of anhydrous citric acid. The use of the two co-solvents has been adequately justified. The finished product is made by Faulding Pharmaceuticals in Australia using an aseptic process. Sterilisation is by filtration, a method that has been justified by the lower assay values and higher degradation levels seen in product that has been autoclaved compared with non-autoclaved product. The high content of ethanol also precludes autoclaving.

The clinical trial formula is identical to the formula proposed for marketing. The container is a Ph.Eur. Type I colourless glass vial closed with a silicone-coated rubber stopper.

Active substance

Paclitaxel is extracted from the leaves, twigs and needles of *Taxus X media* 'Hicksii', an ornamental yew. Clinical studies were carried out using paclitaxel isolated from a different species, *Taxus brevifolia*. In the specification for paclitaxel, the assay and impurity limits have been tightened, reflecting the higher purity of the active substance produced from 'Hicksii' material. There are no concerns with the impurity profile or stability of active from the two sources. Only 'Hicksii' material will be used for the production of Paxene.

There are eleven potentially related substances, two of which have not been seen above 0.1% and are therefore not included in the specification. The limits in the specification for the impurities have been tightened and are justified by toxicology studies. The analytical methods are adequately validated.

The proposed specifications are supported by the available batch analysis results (n = 22 for brevifolia, and n = 4 for 'Hicksii').

The stability studies show that paclitaxel is stable. The proposed retest period of 12 months is acceptable.

Other ingredients

Polyoxyl castor oil and anhydrous citric acid comply with the relevant monographs in Ph. Eur., while ethanol complies with the monograph in BP. The use of polyoxyl castor oil has been justified. On the basis of batch analysis data and the fact that ethanol and citric acid have anti-microbial properties testing for bioburden and endotoxins is not necessary.

Finished product

Paclitaxel is dissolved in ethanol. Citric acid is added to this solution followed by the required quantity of polyoxyl castor oil. With each addition the solution is mixed. The bulk is adjusted to weight with ethanol and the solution is bubbled through with nitrogen. Validation includes in-process and product release test results, justification of manufacturing times, bio-burden limits, filter suitability and media fill trials.

The product is manufactured in a facility that holds the necessary Manufacturing Authorisation.

A single, validated assay method is used for identity, content and related impurities. The pH is controlled around the pH of greatest stability. A limit on moisture is included to limit hydrolysis of paclitaxel. The endotoxin test will be performed according to the Ph. Eur. method. The proposed limits are well below the calculated Endotoxin Limit Concentration. Sterility will be done according to the Ph. Eur., including 14 days of incubation.

The impurity limits in the product specifications are justified by toxicology studies. The batch analysis results (n=9) confirm satisfactory uniformity of the product at release and indicate reliable and consistent performance of the product in clinical use.

The finished product specifications are acceptable. The process has adequately been validated.

A two-year shelf life for the finished product when stored below 25°C, protected from light, is acceptable.

Solution for infusion prepared as recommended should be used immediately or be stored at 2-8°C for not more than 24 hours (see SPC).

3. Toxico-pharmacological aspects

Pharmacodynamics

The active ingredient of Paxene, paclitaxel, is a Pacific Yew tree (*Taxus brevifolia*) derivative with cytotoxic activity.

In vitro studies

Paclitaxel has been shown to inhibit the growth of KS *in vitro*. Four cell lines were used; KSY-1 and KS6-3 (primary culture) isolated from AIDS patients, KS-SLK isolated from a HIV-negative patient and human umbilical vein endothelial cells (HUVEC) infected with human herpes virus 8 (or KS related herpes virus, HHV-8 or KSHV). In a cell proliferation assay, placebo treated cells were unaffected whereas proliferation was suppressed in a dose related manner in KSY-1 and HUVEC-KSHV cells treated with over 0.5 ng/ml Paxene (IC_{50} ≤2.5 ng/ml). The KS6-3 cells were also growth inhibited (IC_{50} ≥10 ng/ml), but the KS-SLK cells were unaffected.

In vivo studies

In an additional *in vivo* study, KSY-1 cells were implanted sc in athymic mice, the next day the animals were treated with Paxene at one of the following doses: 0, 5, 10 or 20 mg/kg ip. Tumour growth was reduced on day 7 at all doses and on day 14 at ≥10 mg/kg. Problems arise in the interpretation of this

study; deaths between days 1 and 4 resulted in low group sizes, only one animal per treatment group could be assessed on days 4 to 14. These data suggest the potential efficacy of paclitaxel in the proposed indication, AIDS-KS.

General pharmacodynamics

Paclitaxel has been the subject of much study since it was first isolated in 1971. It is proposed that paclitaxel promotes polymerisation of tubulin dimers into micro-tubules and stabilises them by preventing de-polymerisation. This inhibits the reorganisation of the micro-tubule network and blocks mitosis. Paclitaxel has also been implicated in the induction of apoptosis. The anti-neoplastic activity of paclitaxel has been demonstrated against a wide variety of tumour types, *in vitro* and *in vivo*, e.g. bladder, brain, breast, cervix, colon, ovary, lung, leukaemia.

Adverse cardiovascular effects were seen in one dog study, i.e. tachycardia, vasodilation, hypotension and collapse immediately post-dose (9 mg/kg iv), but these were not fatal. It is noted that Cremophor EL, the vehicle, has been associated with similar effects in dogs. Cardiovascular effects are reported *in vitro* (concentration dependant arrythmias in cardiac cell cultures) and clinically (transient asymptomatic bradycardia). Sensory neurotoxicity in mice and rats after iv or sc administration has been reported.

Pharmacokinetics

The pharmacokinetics of paclitaxel was investigated in rats, dogs and man. Paxene is to be administered iv, hence most of the studies used this route. Following dissipation of the vehicle, which briefly increases the solubility of paclitaxel in plasma, paclitaxel is 60-70% plasma protein bound in rats. Exposure in rats is supra-proportional to dose, implying that adequate exposures were achieved in pivotal toxicity studies. Dose-related increases in plasma levels were seen in dogs, exposure did not change significantly after six weekly iv doses.

Paclitaxel is widely distributed in the rat, primarily to the GI tract, GI tract contents, liver and testes. Co-administration of Cyclosporin A has been shown to increase bioavailability in rats suggesting the involvement of CYP3A4 in its metabolism. Metabolism studies were not done in the rat nor were the metabolites identified. It is suggested that there are qualitative and quantitative inter-species differences in paclitaxel metabolism and that further studies in this area would not yield any useful information. The need for this information is somewhat superseded by studies in man which suggest CYP2C8 and CYP3A4 involvement, the main metabolite being 6α-hydroxy-paclitaxel.

The half-life of paclitaxel is 6-18 hours in rats, 8-11 hours in dogs and 9-25 hours in man. In rats paclitaxel is excreted in the urine as polar metabolites (9% of administered dose) and in the faeces, mainly as the parent compound (80% of administered dose). It is not known if paclitaxel is excreted in the milk, this is reflected in the SPC.

Toxicology

Single dose toxicity

Single dose toxicity studies were carried out in rats and dogs. Observations in rats included lethargy, piloerection, soft faeces, tremors and prostration post-dose. Observations in the dog included erythema, oedema, tachycardia, hypotension, vomiting and diarrhoea. Lesions seen post-mortem were mild to severe and mainly in areas of high tissue turn-over (e.g. GI tract, bone marrow, testes). The only irreversible finding was of diffuse degeneration and necrosis of testes (seminiferous tubules), often accompanied by degeneration of the epididymis, in both species.

Repeated dose studies

Similar observations were made in repeated dose toxicity tests in rats and dogs. There were additional haematological effects, with a fall in most haematological parameters, lymphoid degeneration and extra-medullary haematopoiesis in the liver and spleen. Comparability was shown between *T. brevifolia* (bark) and *T. media X 'Hicksii'* (biomass) derived paclitaxel in rodents and dogs. Many of the clinical signs are attributed to the vehicle (Cremophor EL) as they are common to vehicle-control and low-dose-paclitaxel animals. When an intermittent administration protocol was used, to mimic the clinical use, these signs were seen to decrease in intensity and duration.

Genotoxicity

Two *in vitro* and one *in vivo* genotoxicity tests were carried out. Paclitaxel in DMSO tested negative in the bacterial reverse mutation assay (*S. typhimurium* and *E. coli*) and the mammalian cell forward mutation assay (CHO cell line). In the mouse micronucleus assay no mortality or adverse clinical signs were seen. A dose related increase in micronucleated polychromatic erythrocytes was seen compared to controls. Paclitaxel is classified as an *in vivo* genotoxin under the conditions of this assay.

Carcinogenicity

Carcinogenicity studies are not required in this case.

Reproductive and development toxicity studies

A developmental study was carried out in rats. Dose-related events included: reduction in body weight gain, alopecia, increased resorptions and post-implantation losses, reduced live pup birth weight, retarded foetal ossification, increased incidence of cervical rib at 7th cervical vertebra, two incidences of dilation of the lateral ventricles of the brain. The maternal and developmental NOEL was 0.3 mg/kg/day (day 7-17 of the gestation).

A full reproductive and developmental toxicity programme is not required as cytotoxic/cytostatic drugs are assumed to cause reproductive disturbances (see the CPMP Note for Guidance on the preclinical evaluation of anticancer medicinal products [CPMP/SWP/997/96]). Paxene is contra-indicated in pregnancy.

Local tolerance

To assess intra-vascular and/or extra-venous irritation potential, Paxene (1.2 mg/ml, 4× the clinical concentration) was infused into the left ear vein (3 mg/2.5 ml/kg) or left ear peri-venous tissue (0.6 mg/0.5 ml) of NZW rabbits. For control purposes, the same volume of 0.9% (w/w) NaCl was infused in the right ear. The sites were observed for 48 hours followed by necropsy and histopathology. Mild irritation (erythema, vascular dilatation) was seen at all sites, including controls, within 15 min of infusion and lasting up to 48 hours. The irritation potential of Paxene is within acceptable limits.

Special toxicity studies

The human blood compatibility of Paxene was determined *in vitro* using haemolysis and erythrocyte aggregation tests. Undiluted vehicle and concentrations ≥0.3 mg/ml paclitaxel caused haemolysis and crenation of erythrocytes. Erythrocyte aggregation and blood clotting were seen at 0.9 mg/ml paclitaxel. Maximally diluted vehicle and concentrations of paclitaxel <0.3 mg/ml were compatible with human whole blood.

Ecotoxicity/Environmental risk assessment

The predicted environmental concentrations of paclitaxel are below 1 ppb and it was concluded that there is no environmental risk from the use, storage and disposal of paclitaxel from Paxene.

4. Clinical aspects

One phase II trial has been conducted in AIDS-KS recruiting a total of 107 patients (all received paclitaxel). In addition safety data are available for a further 436 patients from applicant sponsored Phase I, II, III studies of Paxene in ovarian, breast and non-small cell lung cancer (NSCLC).

The clinical trials were performed according to GCP standards and agreed ethical principles.

Clinical pharmacology

Pharmacodynamics

Mechanism of action

Paclitaxel is a tubulin active anticancer medicinal product with a broad spectrum of antitumoural activity. Apart from this, additional dynamic properties make the substance interesting in the treatment of KS. KS has been described as a model for a growth factor driven tumour, characterised by

prominent neo-angiogenesis. A human herpes virus (HHV-8) has also been implicated in the pathogenesis of KS. Paclitaxel has been reported to exert direct, i.e., effects not mediated by cytotoxicity, anti-angiogenic properties and may also give rise to phosphorylation of HHV-8 induced bcl-2 with consequent tumour cell apoptosis.

Dose finding studies

No dose-finding studies with Paxene have been conducted.

Pharmacokinetics

The studies that have been performed are summarised in Table 1.

Table 1

Number	Report no	Design Dose regimen	Subjects
1	IX-110-081	Open, multicenter 100 mg/m² 3-hour infusion every other week	KS 19 males 28-55 years
2	IX-100-081	Open, dose-escalation 3-hour infusion every third week	NSCLC 14 males, 2 females 135 mg/m² n=3 175 mg/m² n=6 200 mg/m² n=5 225 mg/m² n=2 48-74 years
3, 4	IX-107-081 IX-108-081	Open, multicenter 3- or 96-hour infusion every third week	Metastatic breast cancer and ovarian cancer 17 females 175 mg/m² n=8 140 mg/m² n=4 105 mg/m² n=4 79 mg/m² n=1 45-71 years
5	Tax 1/92	Open, multicenter 175 mg/m² 3-hour infusion every third week	NSCLC 8 males, 3 females 45-72 years
6	Tax 2/92	Open, multicenter 175 mg/m² 3-hour infusion every third week	Advanced breast cancer 13 females 35-67 years
7	IX-103-137	Open, 175 mg/m², single 3-hour infusion	Cancer patients 6 males, 14 females 24-75 years

The pharmacokinetic fate of paclitaxel is concentration-dependent. In AIDS-KS patients, the pharmacokinetics of Paxene are non-linear at doses ≥ 100 mg/m^2.

Based on *in vitro* studies the degree of plasma protein binding of paclitaxel has been reported to range from 88% to 98% and paclitaxel is stated to be predominantly bound to albumin and α1-acid glycoprotein. In spite of this high protein binding, paclitaxel is widely distributed to tissues.

Following an intravenous dose of 100 mg/m² given as a 3-hour infusion to 19 patients with AIDS-related Kaposi's sarcoma, the maximum concentrations ranged from 761 to 2860 ng/ml (mean 1,530) and average area under the plasma concentration versus time curve (AUC) was 5619 ng hr/ml (range 2,609- 9,428). Clearance was 20.6 l/h/m^2 (range 11-38) and the volume of distribution was 291 l/m^2 (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

Renal excretion plays a minor part in the total elimination of paclitaxel, less than 10% of the dose has been reported to be excreted as unchanged drug. The major elimination pathway is metabolism

followed by biliary excretion: in six patients 39% to 87% of an intravenous dose (175 mg/m²) was excreted in faeces and, on average, only 10% of the dose was excreted as unchanged paclitaxel. Several metabolites have been detected but only three of these metabolites have been identified: 6α-hydroxy-paclitaxel, 3'p-hydroxy-paclitaxel and 6α, 3'p-dihydroxy-paclitaxel. 6α-hydroxy-paclitaxel is the major component excreted in faeces.

In vitro studies have shown that CYP2C8 and CYP3A4 are involved in the formation of 6α-hydroxy-paclitaxel and 3'-p-dihydroxy-paclitaxel, respectively.

The antitumour activity of paclitaxel metabolites has not been exhaustively investigated. Although the levels of these metabolites are lower than for paclitaxel, the extent of protein binding is unknown. Theoretically the metabolites could contribute to the antitumour activity. However, the effect is likely to be less than for the parent compound.

Special populations

No controlled studies have been presented which investigate the effects of impaired organ function, age, gender or race. This information is included in section 4.2 of the SPC.

Safety and efficacy in children have not been established and Paxene is not recommended for paediatric use.

Interaction studies

No formal interaction studies have been performed. It is not considered feasible to conduct formal drug interaction studies in AIDS-KS patients given the numerous concomitant medications and the inability to change or discontinue anti-HIV therapy in such patients.

Since paclitaxel is metabolised by cytochrome P450 3A4 and 2C8, caution should be exercised with other medicinal products known to inhibit or induce these enzymes, as they may affect the pharmacokinetics of paclitaxel. In addition, as microsomal levels of CYP C8 have been reported to vary appreciably in human livers, there may be consequences for the disposition of paclitaxel.

Studies conducted in AIDS-KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir. Consequently, Paxene should be administered with caution in patients receiving these protease inhibitors (PI's).

The use of the PI indinavir did not alter tumour response rates in AIDS-KS patients nor did it significantly alter paclitaxel pharmacokinetics.

Neutropenia seems to be related to the duration of time that plasma concentrations remain at or above a threshold concentration (0.05 and 0.1 μmol/l) rather than directly to AUC or C_{max}. Neuropathy, musculoskeletal toxicity, mucositis and leucopenia have also been related to paclitaxel pharmacokinetics. The relationships are not so clear as for neutropenia but these toxic effects seem to be related to total systemic exposure.

Clinical experience

Efficacy

Dose-response studies

No dose-response study has been performed. With respect to the issue of whether a lower dose may be appropriate, the pivotal trial permitted a dose reduction to 75 mg/m² for patients with severe neutropenia and severe neuropathy and it is encouraging that only 12% of patients required this. Four of these patients had a response recorded prior to dose reduction and four after the dose reduction. Also in view of the response rate in the core population (57%) it is likely that the schedule proposed for licensing is expedient in this population. It is not considered feasible to conduct a randomised, controlled clinical trial in patients who have failed liposomal anthracycline treatment comparing the 100 mg/m² and 75 mg/m² dose. Since 1996, the incidence of AIDS-KS is rapidly decreasing in Europe and North America. A study to demonstrate equivalent efficacy would require over 300 patients in each treatment arm and would currently be impossible to complete in a reasonable timeframe. A study

designed to show lower efficacy at the 75 mg/m² dose might not be ethical considering the outstanding anticancer activity and tolerability shown with the 100 mg/m² dose.

Main study

The efficacy and safety of Paxene were investigated in a single, non-comparative study (IX-110-081) in 107 patients with advanced KS, previously treated with systemic chemotherapy. Patients were given a 3-hour infusion of Paxene 100 mg/m² administered every 14 days for at least 2 cycles. The mean age of patients in this study was 38 years and all of the patients were male. Of the 107 patients, 63 patients were considered resistant to liposomal anthracyclines, defined as having progressive disease on a liposomal anthracycline. As liposomal anthracyclines are the only products currently approved for the treatment of advanced AIDS-KS this subgroup of patients is considered to constitute the core efficacy population. The primary endpoint was best tumour response according to modified ACTG criteria (Krown SE, Metroka C, Wernz JC. Kaposi's Sarcoma in the Acquired Immune Deficiency Syndrome: a Proposal for Uniform Evaluation, Response and Staging Criteria. J Clin Oncol 1989;1201-7). Tumour response is considered to be a relevant efficacy measure in the assessment of clinical benefit in patients with KS.

The evaluability of efficacy depends to a large extent on whether the use of effective antiretroviral therapy is regarded as a confounding factor. Because the possibility exists for a pharmacodynamic interaction between contemporaneously introduced, effective antiretroviral therapy and "specific" anti-KS treatment, it should be considered that Paxene efficacy is evaluable only in patients on stable "long-term" antiretroviral therapy prior to and during Paxene treatment.

There were no differences in demographic characteristics between the total population and the subset resistant to liposomal anthracycline-therapy. All of the patients were adult males with a mean age of 38.0 $\pm$ 6.6 years. About half of all patients where white and one-third were white-Hispanic.

All patients had advanced AIDS-KS: 81.3% had ≥ 25 mucocutaneous lesions, 35.5% had visceral involvement and 52.3% had symptomatic lymphoedema. The Karnofsky performance status was ≥ 60 for all patients as this was an entry criterion. Most patients were poor risk based on tumour burden, immune status and systemic involvement based on the ACTG recommended staging classification.

Table 2: Disease stage at baseline

	Core Patients (N=63)		All Patients (N=107)	
	Good Risk	**Poor Risk**	**Good Risk**	**Poor Risk**
Tumour	9 (14%)	54 (86%)	17 (16%)	90 (84%)
Immune	8 (13%)	55 (87%)	17 (16%)	90 (84%)
Systemic	13 (21%)	50 (79%)	19 (18%)	88 (82%)

Results study IX-110-081

59% of core patients and 53% of all patients completed more than 10 cycles. The overall success rate (complete or partial response) after 15 cycles of treatment was 57% (CI 44-70%) in liposomal anthracycline-resistant patients and 56% in the total population (see Table 3).

Table 3: Best tumour response to Paxene

Category	No. of patients	Best response [a]				
		Success [b]	**Complete**	**Partial**	**Stable**	**Progression**
Core patients	63	36 (57.1%)	3 (4.8%)	33 (52.4%)	14 (22.2%)	13 (20.6%)
All patients	107	60 (56.1%)	4 (3.7%)	56 (52.3%)	25 (23.4%)	22 (20.6%)

a: Independent reviewer assessment.

b: Success is defined as complete response or partial response.

More than half of the responses were apparent after the first three cycles of treatment with no important differences between the total population and the core subset.

While spontaneous regressions have occurred in patients with classic KS, this is unlikely to occur in AIDS-KS, which is a more aggressive form of the disease. In addition it is unlikely that patients having failed one or more previous chemotherapeutic regimens would respond spontaneously in the percentage seen in this study (57% of the core patients).

Further subset analyses showed consistency of response in core patients regardless of initial TIS staging, number of previous chemotherapies and previous or concommittant PI use.

In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a PI (55.6%) and those who received one at least 2 months prior to treatment with Paxene (60.9%). Patients who started PI's within 2 months of treatment with Paxene or within the first 10 cycles had a lower response rate (48.1%), but 3 of the 13 patients who responded did so prior to the initiation of PI's. Of the four patients who commenced PI's after cycle 10, all 4 had responded prior to this cycle. In summary, 12 of 36 responses occurred prior to the introduction of PI's or in patients who did not receive PI's.

When all 107 patients are considered, the response rate is lower (32%) in those who did not receive PI's compared to those who started at least two months before the study (58.1%) or those who started PI's during the study (58.5%). In this group, 24 of 60 responses occurred prior to the introduction of PI's or without PI treatment.

The applicant reports that there was an obvious temporal relationship between the onset of response and initiation of Paxene therapy in the core patient group ($p=0.0002$) and all patients ($p<0.0001$). Responses generally occurred within four cycles of initiation of Paxene (median 48.5 days).

In addition, an analysis of time-to-event and survival by PI use has been provided. Among core patients, there was no association between time to response and time to disease progression, treatment failure and survival time and the use of a PI. Among all patients, there was a trend for survival to be longer in patients who received PI's and this is consistent with the published literature on PI's.

Thus in both the core group and all patients, it is likely that the response can be attributed to Paxene as responses occurred prior to the introduction of PI's and in patients who did not receive PIs.

CD_4 counts at baseline were collected as part of the study protocol. Data were available for 102 patients in the all patients population and 60 patients in the core efficacy population. In this subset of the core efficacy population, 32 patients (53.3%) had a CD_4 count of 0-50 cells/mm³, 20 patients (33.3%) had a CD_4 count of 50-200 cells/mm³ and 8 patients (13.3%) had a CD_4 count >200 cells/mm³. Table 4 reports the response rate for patients with baseline CD_4 count of 0-50 versus ≥100 cells/mm³, for patients with data available falling into either category. These data indicate that even patients with a CD_4 count less than 50 had a significant response rate.

Table 4: Best response by CD4 baseline count

Population	CD4	Total no. of patients	Best response				
			Success (CR or PR) N (%)	Complete (CR) N (%)	Partial (PR) N (%)	Stable (S) N (%)	Progression (PD) N (%)
Core patients	{0-50} {≥100}	32 18	15 (46.9) 12 (66.7)	0 (0.0) 3 (16.7)	15 (46.9) 9 (50.0)	7 (21.9) 5 (27.8)	10 (31.3) 1 (5.6)
All patients	{0-50} {≥100}	57 32	26 (45.6) 23 (71.9)	1 (1.8) 3 (9.4)	25 (43.9) 20 (62.5)	16 (28.1) 7 (21.9)	15 (26.3) 2 (6.3)

The effect of PI use on CD_4 counts was compared in 13 patients who received PI's inhibitors and 13 who did not. While individual CD_4 counts increased in some patients treated with PI's, this was not consistently the case.

The median time to progression in the core population is 468 days (95% CI 257-NE). Median survival for Paxene could not be computed, but the lower 95% bound was 617 days in core patients. This is consistent with the view that Paxene does not have negative effects on survival. It is not considered

feasible to conduct a study to investigate the effects of Paxene on survival as there is no comparative agent for multi-resistant patients who have failed liposomal anthracyclines. Historical controls cannot be used, because of the changing nature of both AIDS and AIDS-KS.

The total Symptom Distress Scale (SDS) score in the core efficacy population decreased significantly during treatment ($p \leq 0.001$) and mirrored the improvements seen in tumour response. Compared with baseline, there was a significant improvement in the Karnofsky Performance Score.

Safety

Patient exposure

In the main study 107 patients have been enrolled and administered a total of 1,474 courses of Paxene, thereof 57 patients were administered >10 courses. Dosage reductions to 75 mg/m² were recorded in 13 patients. Delays in treatment due to toxicity occurred with 43 (5.4%) of the first 10 cycles and 38 (5.8%) of subsequent cycles. G-CSF was used by close to 50% of the patients during the first cycle, and use ranged between 60 and 70% during cycles 2 to 10, increasing to >80% after cycle 10. There was concern that the use of filgrastim in HIV-positive patients would result in an increase in viral replication, as this has been reported for GM-CSF. However, there are a number of studies in the published literature which indicate that filgrastim is safe and effective in preventing severe neutropenia in patients with advanced HIV infection, and is not associated with an increase in viral replication.

Adverse events, including serious adverse events

Altogether 34 patients died, thereof 15 during the study or within 30 days of dosing. The investigator as being due to Paxene reported only one of the deaths during therapy. There are indications that in at least 7 patients Paxene therapy might have contributed to a shortened survival.

A total of 387 adverse events were judged severe (CTC grade 3 or greater in severity) in all patients. Generally speaking, the frequency and distribution of severe adverse effects reported in the core population was similar to that of the group as a whole. Of the 226 severe adverse events reported in the subset of patients, 54 were life-threatening. The most common related adverse event was neutropenia, which was severe in 65 cases. Severe alopecia was seen in 11 cases. Other severe adverse events considered related to Paxene were thrombocytopenia (9 cases), sepsis (3 cases), diarrhoea (4 cases) and neuropathy (2 cases).

An overview of observed adverse events is presented in Table 5.

Table 5: Adverse events in descending order of incidence in the AIDS-KS study (protocol IX-110-081; N=107) for those judged related to Paxene

Adverse event	Overall incidence N (%)	Related to drug N (%)
Neutropenia	69 (64.5%)	68 (63.6%)
Alopecia	66 (61.7%)	66 (61.7%)
Asthenia	69 (64.5%)	46 (43.0%)
Neuropathy [a]	50 (46.7%)	28 (26.2%)
Nausea	51 (47.7%)	28 (26.2%)
Diarrhoea	72 (67.3%)	23 (21.5%)
Rash	50 (46.7%)	21 (19.6%)
Myalgia	27 (25.2%)	19 (17.8%)
Anaemia	25 (23.4%)	15 (14.0%)
Leucopenia	17 (15.9%)	15 (14.0%)
Hiccup	22 (20.6%)	14 (13.1%)
Vomiting	32 (29.9%)	14 (13.1%)
Arthralgia	20 (18.7%)	14 (13.1%)
Thrombocytopenia	14 (13.1%)	11 (10.3%)
Taste perversion	10 (9.3%)	8 (7.5%)
Anorexia	43 (40.2%)	7 (6.5%)

Pruritus	22 (20.6%)	7 (6.5%)
Pain	43 (40.2%)	6 (5.6%)
Dyspepsia	12 (11.2%)	5 (4.7%)

a: Neuropathy includes the terms neuropathy, paresthesia, peripheral neuritis and hypesthesia.

Although the data are limited, an analysis of adverse events by PI use did not show any significant differences in the incidence of all grades of events or severe events. Certain PIs (ritonavir and nelfinavir) interfere with the clearance of paclitaxel and so may enhance the toxicity. A reduction in the dosage of Paxene may be required, as indicated in the SPC.

Haematological toxicity

Haemoglobin, hematocrit, platelet, leukocyte and neutrophil counts all declined during the study and in the majority of cases these changes were related to Paxene administration. However, there was no downward trend in the values with additional dosing during the study.

Filgrastim was required by 85% of patients by cycle 15 to minimise neutropenia.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Pre-clinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence of the potential efficacy of this product in the proposed indication. The data with regard to the pharmacokinetics are satisfactory. Overall the toxicology programme revealed that paclitaxel is mutagenic *in vivo*, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. The carcinogenic potential of paclitaxel has not been studied. Paclitaxel at low doses of 0.6 mg/kg/day produced low fertility and foetal toxicity in rats. Animal studies showed apparently non-reversible, adverse effects of paclitaxel on the male reproductive organs at clinically relevant exposure levels. This information has been included in the SPC.

Efficacy

The efficacy of Paxene in AIDS-KS patients who have failed to respond to liposomal anthracyclines has been demonstrated in terms of tumour response, time-to-event data and clinical benefits. Notwithstanding differences in the clinical trials, the tumour response rate associated with Paxene is superior to that reported for Caelyx (Stewart S, Jablonowski H, Goebel FD, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin in the treatment of AIDS-related Kaposi's sarcoma. J Clin Oncol 1998;683-91) and DaunoXome (Gill PS, Wernz J, Scadden DT et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996; 14:2353-64), the only treatments currently available for advanced AIDS-KS.

Safety

The safety profile of Paxene for the treatment of AIDS-KS was considered difficult to assess particularly in the absence of comparative data. Myelosuppression is the major dose-limiting undesirable effect of paclitaxel and this is usually manifest as neutropenia. Paxene was associated with 65% incidence of severe neutropenia and a 14% incidence of neutropenic fever. There is an increased risk of infections in patients treated with Paxene, and infections related to Paxene may have contributed to three of 15 deaths that occurred on study. Filgrastim (G-CSF) was used by more than 50% of patients in any cycle. Notwithstanding the difficulties in comparing studies, the incidence of severe neutropenia appears to be higher in Paxene-treated patients than that reported for Caelyx, DaunoXome and ABV (doxorubicin, bleomycin, and vincristine).

In support of Paxene, few patients (6/107) discontinued the study due to Paxene-related adverse events, only 4% of cycles were delayed because of neutropenia, only 12% of patients required a reduction in the dose due to toxicity, and >55% of patients continued on maintenance therapy.

Benefit/risk assessment

Based on the available data on quality, safety and efficacy, the CPMP considered by consensus the benefit/risk profile of Paxene in the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy to be favourable.

6. Aditional indication:

1 Introduction

Paxene (6mg/ml concentration for solution for infusion) contains the cytotoxic active substance paclitaxel, a naturally occurring product derived from the yew tree.
Paxene was centrally approved in the EU for the treatment of AIDS-related Kaposi's sarcoma in patients who have failed prior liposomal anthracycline therapy in July 1999. Paxene is also marketed in the USA under the name Onxol for the indications: breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy and advanced ovarian cancer. Another paclitaxel, Taxol, is approved in several EU countries since 1993.

The most effective single agents in the treatment of metastatic breast cancer are the taxanes and the anthracyclines. However, currently there is no established standard therapy. Paclitaxel is the first of the taxanes. It is integrated in combination treatment regimens for treatment of metastatic breast cancer and combination therapy with doxorubicin and paclitaxel is superior to single-agent therapy in terms of response. However, no survival advantage has been observed. As it has not been demonstrated to have benefit over conventional chemotherapy for advanced breast cancer it is therefore, indicated as 2nd line for patients who have failed anthracycline therapy.

Most of the patients diagnosed with ovarian cancer of epithelial origin have advanced disease at presentation. The most commonly adopted regimen in first-line chemotherapy consists of a combination of a platinum (cisplatin or carboplatin) and an alkylating agent (usually cyclophosphamide). Whatever type of chemotherapy is chosen, standard treatment usually yields clinical objective response rates (complete and partial) of 60 to 70% and 5-year survival rates of 10 to 20%, with median survival of about 24 months in most studies.

The MAH applied for 2 Type II variations for Paxene for the additional indications of:
- 2nd line treatment of metastatic breast cancer in patients who have failed or are not candidates for standard anthracycline -containing therapy i.e. same indication as the one approved for Taxol.
- metastatic ovarian cancer after failure of platinum-containing combination therapy without taxanes.

These applications are intended to extend the pharmacotherapeutic repertoire in refractory metastatic breast and ovarian cancer to provide an alternative to marketed taxane preparations.

The application for the indication of metastatic breast cancer was initially based on a single clinical trial conducted by the applicant: Phase III study in patients with refractory metastatic breast cancer (Protocol IX-107-081 Mettinger et al. 2000a). In this trial the efficacy and safety of Paxene was determined after administration of 175mg/m^2 via 3-hour infusion and of 140mg/m^2 via 96-hour infusion, both repeated at 3-week intervals.

The application for the indication of metastatic ovarian cancer was initially based on a single clinical trial conducted by the applicant: Phase III trial of 3-hour infusion of Paxene (Paclitaxel) in patients with refractory ovarian cancer with rescue to 96-hour infusions on failure of 3-hour infusion (Protocol IX-108-081 Mettinger et al. 2000b)

In response to the CPMP request for supplementary information, the MAH submitted the original clinical data of paclitaxel, with consent of BMS (Taxol), in support of the new indications. In order to demonstrate the scientific relevance of these data, quality issues related to the formulation of paclitaxel had to be addressed.

2 Quality aspects

The Taxol formulation was developed in the early 1980's (50% Cremophor EL (CrEL) and 50% ethanol) as the most suitable vehicle for I.V. administration of the product to humans. A purified version of CrEL (CrEL-P) was introduced into the formulation in the early 1990's to increase the chemical stability of the product (a loss of potency of > 60% after 12 weeks storage at 50°C was discovered when the commercial CrEL was used). The Paxene formulation was developed based on the published information on Taxol (i.e. a 50:50 mixture of CrEL and ethanol). During further optimization, it was found that the addition of 0.2 % citric acid (2 mg/ml) improved chemical stability properties. Without citric acid, a 10% decrease in paclitaxel was observed after storage at 40°C for 7 days. However, the formulation containing 0.02% citric acid showed only 0.07% degradation after the same storage condition (40°C for 7 days).

The information supplied by Norton Healthcare confirms that the two products have essentially the same quantitative and qualitative formulations in terms of active substance and pharmaceutical forms (both products are solutions for injection). The MAH was not required to submit a bioequivalence study as the product is to be administered as an aqueous IV solution containing the same active substance in the same concentration as the currently authorised product (Taxol). However, Cremophors (Polyoxyethylated castor oil) are prone to micelle formation. Therefore the possibility was raised that differences between the two formulations (purified Cremophor in Taxol as opposed to addition of citric acid in Paxene) might affect micellar formation in vivo thereby altering the kinetics which might have implications for safety assessment of the different products.

Micelle formation is a property of surfactants and takes place when a surfactant, in aqueous solution, reaches its critical micelle concentration (CMC). The CMC is a unique character of surfactants, which can be determined by measuring changes in various physical properties such as surface tension, conductivity, light scattering, osmotic pressure and the solubility of a water-insoluble dye. Surface tension and light scattering are commonly used to measure the CMC. These in vitro techniques were used in four studies to evaluate micelle formation of Paxene (containing Cremophor EL, ethanol and citric acid) and Taxol (containing purified Cremophor EL and ethanol) formulations in media simulating the physiological environment, including solutions recommended for the clinical administration of Paxene and Taxol. The studies also investigated the effect of citric acid on micelle formation. Comparative analysis of the CMC, molecular mass of micelles and particle size of micelles was carried out for Paxene and Taxol in saline solution and/or phosphate buffered solution (PBS: pH 7.4) and/or 5% glucose solution. The results for CMC are summarised in Table1.

Table 6.1: CMC of Paxene and Taxol in Different Media

Media	CMC (mg/ml)	
	Paxene	Taxol
Water	0.0307 ± 0.0014	0.0387± 0.0008
Saline Solution	0.0610 ± 0.0047	0.0654 ± 0.0032
PBS (pH7.4)	0.0542 ± 0.0042	0.0528 ± 0.0013
5% Glucose	0.0550 ± 0.0006	0.0573 ± 0.0016

Molecular Mass of micelles formed in Paxene was determined as 322,000, in Taxol was 319,000 and placebos of Cr-EtOH with or without citric acid was 293,000 and 274,000 respectively.

Measurements of the particle size of micelles for Paxene and Taxol by DLS using a He-Ne Laser and QELS using a submicron particle sizer further supported the similarity of the two preparations.

Paxene is manufactured with a nitrogen headspace, so the CrEL in the product is exposed only to the nitrogen environment within the closed vial thereby minimising any possible oxidation. Oxidation of

CrEL under the micro-nitrogen environment of the closed vial and at the storage condition specified for Paxene is probably an extremely slow process, very unlikely in these circumstances and therefore micelle formation of CrEL will be unaffected during the specified shelf life of Paxene .

3. Clinical aspects

The variation was initially submitted based on the clinical trials described in sections 3.2 and 3.3. As a response to the CPMP objections the MAH provided original data on Taxol to support its claim for the new indication. The MAH was asked to demonstrate how Paxene is related to Taxol. This was regarded as crucial because the efficacy data from Paxene clinical trials alone, were inadequate to support authorisation of Paxene in the new indications.

3.1. Pharmacokinetics

In Vitro Binding Study in Human Plasma by Equilibrium Dialysis

The non-linear plasma pharmacokinetics of paclitaxel in patients has been well documented. However, the exact mechanism remains to be elucidated. Previous theories suggested that non-linearity was based on saturable distribution and elimination kinetics. A more recenthypothesis proposed that entrapment of paclitaxel in plasma by CrEL, probably in micelles, may contribute to the apparent non-linear plasma pharmacokinetics of paclitaxel. Technology for direct measurement of micelle formation *in vivo* is currently not available. An *in vitro* plasma equilibrium dialysis model (a two-compartment equilibrium dialysis system) was established to assess the influence of CrEL/CrEL-P on the plasma binding of paclitaxel from an infusion solution. According to this model, the fraction of unbound paclitaxel can be estimated by determination of the ratio of the paclitaxel concentration in a compartment containing buffer and the concentration in another compartment containing plasma. This model was used to investigate the effect of CrEL, CrEL-P, and citric acid on the fraction of unbound paclitaxel in human plasma.

The data show that the presence of citric acid has no significant additional effect on the fraction of unbound paclitaxel in the CrEL-P-containing vehicle tested. The fraction of unbound paclitaxel from Taxol (CrEL-P/ethanol) and Paxene (CrEL/citric acid/ethanol) formulations were not significantly different (7.12% and 7.54% respectively).

Table 6. 2: Results of the Fraction of unbound (Fu) Paclitaxel in Human Plasma for Various Formulations

Formulation (Sample Code)	Fu (%)	Con. (µg/ml) Paclitaxel	Con. (mg/ml) CrEL/CrEL-P
Ethanol (A)	**8.86 ± 0.667**	**1,000**	**N/A**
CrEL/ethanol (B)	**6.79 ± 0.663**	**1,000**	**528.0**
CrEL-P/ethanol (C)	7.12 ± 0.525	1,000	527.4
CrEL/citric acid/ethanol (D)	7.54 ± 0.516	1,000	527.0
CrEL-P/ethanol (E)	**5.84 ± 0.403**	**500**	**526.8**
CrEL-P/citric acid/ethanol (F)	**5.83 ± 0.199**	**500**	**526.8**

The MAH provided pharmacokinetic studies together with an addendum to the Expert Report summarising all relevant PK data to provide assurance that the kinetic characteristics are similar.

A total of six pharmacokinetic studies (TAX-1/92, TAX-2/92, IX-100-081, IX-107&108-081, IX-110-081 and IX-103-137) were carried out with Paxene. The full study reports were provided in the original marketing authorisation application in 1997 and responses to the CPMP List of Questions in 1998. The six studies involved 97 patients (48 males and 49 females) with non-small cell lung cancer, breast cancer, ovarian cancer, metastatic cancer and AIDS-KS.

The results of the key pharmacokinetic (PK) parameters in plasma from these studies are summarised in Table 3. Comparative analysis of these (C_{max},, $C_{max,}$, AUC_{last}, $AUC_{N,}$ CL and V_{ss}) was performed

with published Taxol data over a wide dose range. C_{max} and AUC data were normalised to a 100 mg/m^2 dose ($C_{max,N}$ and AUC_N).

Table 6. 3. Results of Key PK Parameters from Studies TX-1/92, TAX-2/92, IX-100-81, IX-107-081/IX-108-081, IX-110-081 and IX-103-137

Study	Dose (mg/m^2)	N	C_{max} (µg/mL)	AUC_{last} (µg.h/mL)	AUC_∞ (µg.h/mL)	CL (L/h/m^2)	Vss (L/m^2)	V_β (L/m^2)
TAX-1/92	**175 x3h**	**11**	**3.59 ± 2.26**	**12.6 ± 5.89**	**N/A**	**16.3 ± 6.66**	**150 ± 118**	**N/A**
		14	**4.12 ± 2.23**	**13.8 ± 5.92**	**N/A**	**15.1 ± 6.48**	**126 ± 114**	**N/A**
TAX-2/92	**175 x 3h**	**13**	**3.89 ± 1.22**	**14.1 ± 4.53**	**N/A**	**13.1 ± 4.5**	**123 ±41**	**N/A**
IX-100-081	**135 x 3h**	**3**	**5.69 ± 2.71**	**14.4 ± 8.87**	**N/A**	**10.8 ± 5.80**	**14.4 ± 5.6**	**22.4 ± 6.10**
	175 x 3h	**6**	**7.85 ± 3.46**	**22.5 ± 9.79**	**N/A**	**8.65 ± 4.7**	**22.1 ± 11.3**	**41.3 ± 31.8**
	200 x 3h	**5**	**20.0 ± 26.0**	**40.8 ± 27.0**	**N/A**	**5.4 ± 2.6**	**40.9 ± 45.0**	**68.0 ± 62.4**
		4	**8.44 ± 3.21**	**27.50 ± 6.47**	**N/A**	**6.46 ± 1.81**	**53.8 ± 45.2**	**85.3 ± 63.6**
	225 x 3h	**2**	**17.9 ± 4.38**	**93.9 ± 68.5**	**N/A**	**2.6 ± 7.1**	**53.1 ± 34.0**	**77.0 ± 21.8**
IX-107-081	**175x 3h**	**8**	**4.21 ± 1.95**	**12.6 ± 6.59**	**13.2 ± 6.81**	**20.4 ± 17.4**	**136 ± 161**	**274 ± 268**
IX-108-081	**140 x 96h**	**4**	**0.122± 0.099**	**5.89 ± 1.62**	**5.52 ± 1.91**	**26.8 ± 9.62**	**292 ± 317**	**664 ± 738**
	105 x 96h	**4**	**0.102± 0.068**	**4.08 ± 1.30**	**4.43 ± 1.26**	**24.9 ± 5.84**	**608 ± 302**	**916 ± 680**
	79 x 96h	**1**	**0.068**	**5.96**	**8.19**	**9.7**	**671**	**740**
IX-110-081	**100 x 3h**	**19**	**1.53 ± 0.55**	**5.06 ± 1.87**	**5.62 ± 2.09**	**20.5 ± 8.33**	**291 ± 153**	**N/A**
IX-103-137	**175 x 3h**	**20**	**3.65 ± 0.87**	**12.9 ± 3.06**	**13.5 ± 3.22**	**13.7 ± 3.23**	**105 ± 81.8**	**370 ± 281**

Comparison of PK Parameters Following 3 Hours Infusion of Taxol (Publications) and Paxene (Study No. IX-110-081, IX-100-081, TAX-1/92, TAX-2/92, IX-107-081/IX-108/081, IX-103-137, and Nannan Panday et al)

Dose [mg/m^2] Reference	N	Cancer Type	C_{max} [µg/mL]	$C_{max,N}$ [µg/mL /100mg]	AUC_{last} [µg•h/mL]	AUC_N [µg•h/mL /100mg]	CL [L/h/m^2]	V_{SS} [L/m^2]
75 mg/m^2								
IX-110-081	1[&]	Kaposi's Sarcoma	1.47	1.96	7.41	9.88	8.7	160
100 mg/m^2								
IX-110-081	19	Kaposi's Sarcoma	1.53	1.53	5.06	5.06	20.5	291
Mross et al. 2002	13	Various	1.26	1.26	5.18	5.18	22.8	138
135 mg/m^2								
IX-100-081	3	NSCL	5.69	4.21	14.4	10.7	10.8	22.4
Huizing et al. 1993[§]	7	Ovarian	2.17	1.61	8.00	5.93	17.6	98.3
Gianni et al. 1995[§]	4	Breast/Ovarian	2.82	2.09	9.31	6.90	14.8	NA
175 mg/m^2								
TAX 1/92[§]	11	NSCL	3.59	2.05	12.6	7.22	16.3	150
TAX 2/92[§]	13	Breast	3.89	2.22	14.1	8.05	13.3	123
IX-107-081/108-081	8	Breast/Ovarian	4.21	2.41	12.6	7.20	20.4	274
IX-103-137	20	Metastatic cancer	3.65	2.09	12.9	7.37	13.7	105

Dose [mg/m^2] Reference	N	Cancer Type	C_{max} [µg/mL]	$C_{max,N}$ [µg/mL /100mg]	AUC_{last} [µg•h/mL]	AUC_N [µg•h/mL /100mg]	CL [L/h/m^2]	V_{SS} [L/m^2]
IX-100-081	6	NSCL	7.85	4.49	22.5	12.8	8.7	41.3
Nannan Panday et al. 1999 (Paxene)	7	Breast/Ovarian	4.27	2.44	14.4	8.25	12.9	NA
Ceruti et al. 1999	10	Breast/Ovarian	5.17	2.95	20.8	11.9	14.4	58.2
Gianni et al. 1995[§]	3	Ovarian	5.04	2.88	15.8	9.03	11.4	NA
Huizing et al. 1993[§]	5	Ovarian	3.65	2.04	14.4	8.20	16.8	99.3
200 mg/m^2								
IX-100-081	4	NSCL	8.44	4.22	27.5	13.8	6.5	53.8
Berg et al. 1995[§]	6	Breast	4.36	2.18	20.5	10.3	10.7	63
210 mg/m^2								
Minami et al. 2001	17	Breast	NA	NA	23.8	11.3	9.7	NA
Schiller et al. 1994	10	Various	5.12	2.44	19.1	9.11	11.9	68
225 mg/m^2								
IX-100-081	2	NSCL	17.9	7.96	93.9	41.7	2.6	53.1
Gianni et al. 1995[§]	15	Breast/Ovarian	6.49	2.88	20.8	9.22	11.6	NA
250 mg/m^2								
Huizing et al. 1995[§]	9	Breast	5.91	2.36	23.1	9.25	NA	49.8
Seidmann et al. 1995[§]	23	Breast	9.05[#]	3.62	NA	NA	NA	NA

NA = Not applicable; NSCL = Non small cell lung

[&] Single patient with hepatic dysfunction and suggested drug interaction;

[#] Predicted from PK modelling

[§] Calculated from molar concentrations (MW=853.9);

Statistical analysis was also carried out based on two-sample z-test using standardised weighted means (assuming normal distribution) to compare the two important PK parameters (C_{max}, and AUC) following a 3-hour infusion of 175 mg/m^2 of Paxene and Taxol (Table 5). Each product mean was calculated as the weighted mean of each study using the given product. For each study the inverse of the corresponding standard error of the mean was used as the mean weight. The z-test was constructed as the difference of product means divided by the square root of the sum of standard errors of the product means. The P values for the C_{max} and the AUC) are 0.8998 and 0.5062. There is no significant difference between Paxene and Taxol in C_{max} an AUC.

Table 6.5: Comparison of Two Key PK Parameters Based on Two-Sample Z-Test Following a 3-hour infusion of Paxene and Taxol at Dose of 175 mg/m^2

Product	Reference	N	Cancer Type	C_{max} (µg/mL)	AUC_{last} (µg.h/mL)
Paxene	TAX 1/92	11	NSCL	3.59±2.26	12.6 ± 5.89
	TAX-2/92	13	Breast	3.89±1.22	14.1 ± 4.53
	IX-107/108-081	8	Breast/Ovarian	4.21±1.95	12.6 ± 6.59
	IX-103-137	20	Metastatic cancer	3.65±0.87	12.9 ± 3.06
	IX-100-081	6	NSCL	7.85±3.46	22.5 ± 9.79
	Nannan Panday et al 1999	7	Breast/Ovarian	4.27±1.3	14.4 ±4.10
Taxol	Ceruti et al 1995[A]	10	Breast/Ovarian	5.17	20.8
	Gianni et al 1995	3	Ovarian	5.04±0.8	15.8 ± 2.56
	Huizing et al 1993	5	Ovarian	3.65±1.1	14.4± 3.55

A: no SD available in the publication and therefore not included in the analysis.

Data from a second independent comparative analysis based on five published PK studies for Taxol and three for Paxene at comparable dose levels (100-, 135-, 175- or 200 mg/m^2 by 3-hour infusion) suggest that the non-linearity of paclitaxel PK previously noted for Taxol is also observed for Paxene following a 3-hour infusion.

3.2. Clinical trials submitted in support of the indication of Metastatic Breast Cancer (MBC)

One pivotal study conducted with Paxene in patients with advanced **breast cancer** was initially submitted:a Phase III trial of 3-hour vs. 96-hour infusions of Paxene (Paclitaxel) in patients with refractory metastatic breast cancer and an assessment of 96-hour infusions in 3-hour failures (Protocol IX-107-081). The trial was designed to compare 3-hour and 96-hour infusions of Paxene in women with metastatic breast cancer, who had failed to respond to at least two prior chemotherapy regimens, one of which had been given for metastatic disease. The dose for the 96-hour infusion regimen, 140 mg/m^2, was based on a paper published by Wilson et al[1] while in the control arm Paxene was administered at a dose of 175 mg/m^2, i.e. the licensed dose of Taxol. The cycle length was 3 weeks for both regimens.

Segment II (Rescue Therapy) was a phase II study with a built in stopping rule. If at least 1 CR/PR was seen in the first 14 patients receiving rescue therapy then patients showing rapid progression on 3-hour infusion would be crossed over to 96-hour. If none of the first 14 patients responded then rescue would be discontinued.

The primary endpoint in both segments was time to progression (TTP) defined as the time from randomisation to documented disease progression or to time of a non-cancer death. The secondary endpoints were the best responses to therapy: Complete response rate (CR), Overall survival and improvement in Quality of Life (QoL) as reported on the Symptom Distress Scale (SDS) analyzed on a scoring system. (Overall survival was defined as time from randomisation to death from any cause. The best response was categorized as success if the patient had either a PR/CR to treatment.) Radiological responses were reviewed and verified by an external panel of independent radiologists.

Results

Primary endpoint -Time to Disease Progression (TTP)
The median times to disease progression were comparable in the two treatment groups 11.14 weeks (3-hour) vs. 12.71 weeks (96-hour) (P=0.3109).

[1] Wilson et al, Paclitaxel in Doxorubicin-refractory or mitozantrone-refractory breast cancer –A phase I/II trial of 96-hour infusion J Clin Oncol 1994 12/8 1621-29

Median Time to Disease Progression (weeks)

Group	Median	Lower 95% CI	Upper 95% CI	P value[a]	P value [b]
3-hour	11.14	8.29	13.14	0.3109	0.5843
96-hour	12.71	8.86	18.14		

a adjusted for baseline differences in KPS, prior anthracycline treatment (none, resistant, non-resistant), region (Nth America vs. Australia and Europe);

b adjusted for measurable/non-measurable disease

Secondary endpoints - best responses to therapy (PR/CR/stable disease):
The tumour response rates were not statistically different 18.5% (3-hour infusion) and 25.2% (96 hour infusion) by Fisher's Exact Test (P=0.1670). The CR rate was 4.7% (8) in the 3-hour and 5% (7) in the 96-hour arm. In patients with measurable disease the response rates were 20.9% and 28% respectively. Another 36.4% and 30.2% of patients had stable disease on Paxene.

Best Tumour Response by Treatment Group (Number (%))

Treatment Group	Complete/Partial	Stable	Disease Progression	P value ITT
3-hour ITT	4/28 (18.5%)	63 (36.4%)	78 (45.1%)	
Measurable (80.3%)	29 (20.9%)	46 (33.1%)	64 (46.0%)	0.1670
96-hour ITT	1/34 (25.2%)	42 (30.2%)	62 (44.6%)	
Measurable (84.0%)	33 (28.0%)	34 (28.8%)	51 (43.2%)	

The best response to Paxene was examined by the most recent prior chemotherapy and the highest category of chemotherapy. The lowest response to Paxene was seen in patients previously treated with anthracyclines. The response to Paxene was higher in the 96-hour treatment group than the 3-hour group when previous therapy was another chemotherapeutic agent.

Overall Survival
Median survival times were comparable in the two treatment groups at 39.7 weeks (3-hour) and 34.7 weeks (96-hour) infusions (P=0.7128).

Median Survival Time (Weeks)

Group	Median	Lower 95% CI	Upper 95% CI	P value[a]	P value [b]
3-hour	39.71	31.0	52.57	0.7128	0.3817
96-hour	34.71	26.14	46.0		

a adjusted for baseline differences in KPS, prior anthracycline treatment (none, resistant, non-resistant), region (Nth America vs. Australia and Europe)

b adjusted for measurable /non-measurable disease

Other Time to event parameters
Time to Response-the median times to response was comparable in the two treatment groups at 6.8 weeks (3-hour) and 9.0 weeks (96-hour) infusion groups respectively.
Duration of Response-the median durations of response was comparable in the two treatment groups at 19.6 4 weeks (3-hour) and 22.0 weeks (96-hour) infusions.

Quality of Life as measured by SDS scores improved significantly in both arms (P<0.05) and the improvement tended to be greater in patients randomised to 96-hour infusions in the total population as well as in patients with bone lesions. Improvement of the combined score for pain, nausea, appetite and fatigue was more consistently observed with 96-hr infusion.

Segment II (Rescue Study) 32/41 (78%) progressed into segment II.
Best Tumour Response-a partial response to Paxene was seen in 17.1% (7/41) of patients (95% CI: 7.2-32.1%). Stable disease was present in 3/41 7.3%. The median time to progression was 49 days (42-88ds). The median survival was 162 days. The median time to response was 64 days. The median duration of response was 103 days. The study was considered too small for further analysis.

Currently, the following dosage is recommended for metastatic breast cancer: 175mg/m2 via 3-hour infusion every 3 weeks. Clinical trials have investigated the administration of paclitaxel every 3 weeks

at varying doses (135-250mg/m2) and schedules (1-3-24- and 96 hour infusions). The 3-hour schedule produced a lower incidence of myelosuppression but more frequent and severe peripheral neuropathy. Prolonged infusion of paclitaxel increase cytotoxicity, and therefore response rates and decreases hypersensitivity reactions.

3.3. Clinical trials submitted in support of the indication Metastatic Ovarian Cancer (MOC)

A single, non-randomised pivotal study conducted by the Applicant with Paxene in patients with MOC was initially submitted: a Phase III trial of 3-hour infusion of Paxene (Paclitaxel) in patients with refractory ovarian cancer with rescue to 96-hour infusions on failure of 3-hour infusion (Protocol IX-108-081).

Patients with ovarian carcinoma who had failed at least one, but not more than two platinum based chemotherapy regimens were eligible for this study. In segment 1 of the study, all patients received Paxene at a dose of 175 mg/m^2 infused over 3 hours every 3 weeks (licensed posology for Taxol for this indication). Patients with progressive disease within 4 cycles on this regimen were eligible for segment 2 and treatment with Paxene 140 mg/m^2 infused over 96 hours every 3 weeks.
Altogether 120 patients were enrolled, the median age was 62 years and 76% of the patients were previously treated with carboplatin (cisplatin 42%).

Efficacy results

Primary endpoint – Progression free survival
The median time to disease progression was 122.5 days (17.5 weeks) (95% CI, 100; 146 days)

Secondary endpoints -

Best Response to therapy (PR/CR/stable disease)

Best Tumour Response, Segment 1

	Complete/Partial Response	Stable Disease
Number (%)	26 (21.7%)	23 (19.2%)
95% CI	14.7%; 30.1%	12.6%; 27.4%

Overall survival.

Median Overall Survival, Segment 1: 403 days (95% CI, 346; 450 days)
Segment II (Rescue study).
Best Tumour Response, Segment 2: Partial Response 1/24, Stable Disease 1/24

3.4. Discussion

One pivotal study conducted with Paxene was submitted for each of the claimed indications. These studies did not meet the requirements of the CPMP PtC on Applications with One Pivotal study for phase III documentation of efficacy in the claimed indication nor were they comparator studies as recommended (CPMP/EWP/205/95 Note for Guidance evaluation of anti cancer medicinal products).
No randomised, comparative study has been submitted to support the licensing of Paxene for the treatment of metastatic carcinoma of the ovary after failure of platinum-containing combination therapy without taxanes. This was not considered acceptable, as there are licensed products available (e.g., topotecan).

Another paclitaxel, Taxol is currently licensed for the treatment of metastatic breast cancer and for first-line therapy and second-line treatment of patients with ovarian cancer failing cisplatin-based therapy. In response to the objections of the CPMP the MAH submitted additional original clinical data on paclitaxel from the MAH of Taxol, BMS. The Applicant demonstrated that the two products have essentially the same quantitative and qualitative formulations in terms of active substance, and pharmaceutical forms. However, differences in formulation between Taxol and Paxene were noted which put in question whether clinical trial results using the Taxol formulation could be extrapolated

and applied to Paxene. The Applciant subsequently convincingly demonstrated that the difference in formulation (addition of citric acid) between the two products does not affect micelle formation *in vivo* therefore the submitted clinical data on Taxol can be considered scientifically relevant to support the claimed new indications for Paxene, and to provide the necessary assurances regarding safety and efficacy.

The submitted data on micelle formation clearly demonstrate that:

- The critical micelle concentration is similar for the Paxene and Taxol formulations.
- The micelles formed from Paxene and Taxol in the stated physiological media are of comparable size and molar mass.
- The use of CrEL and citric acid in the Paxene formulation has no significant effect on micellar structure relative to the Taxol formulation.

The studies using *in vitro* techniques demonstrated equivalence of micelles formed from Paxene and Taxol formulations in physiological solutions or solutions recommended for clinical administration of paclitaxel injections.

The MAH provided data from six pharmacokinetic studies conducted with Taxol and Paxene in the clinically relevant dose range involving 97 patients (48 male, 49 female) with cancer. Comparative analysis of key pharmacokinetic parameters (C_{max}, $C_{max,}$ AUC_{last}, $AUC_{N,}$ CL, and V_{ss}) was performed with published Taxol data over a wide dose range (75-210mg/m$^{2)}$ and provides good evidence that there is no difference in paclitaxel pharmacokinetics, which are non-linear at doses of 175 mg/ m^2 and above, following administration of Paxene and Taxol. This non-linearity, at clinically relevant dose range, has been shown to be due to the excipient CrEL. As CrEL forms micelles *in vivo*, in which paclitaxel is trapped, these micelles act as high affinity drug-transporting sites resulting in a decreased portion of free paclitaxel. Consequently the pharmacokinetic of CrEL is critical to the pharmacokinetics of paclitaxel.

Both the *in vitro* and PK data show that there is no evidence that citric acid and CrEL in the Paxene formulation have a significant effect on the *in vitro* or *in vivo* properties or kinetics of paclitaxel.
Pharmacokinetic data indicate that the kinetics of both Paxene and Taxol follow a similar non-linear fashion. The important characteristics (Cmax and AUC) for both are comparative at the same dose level. The corresponding data on total clearance at each dose level also show similarity between Paxene and Taxol.

In conclusion, the comparative PK analysis indicates the plasma PK profile of paclitaxel following administration of Paxene is identical to that observed following administration of Taxol. This suggests that the excipients present in these formulations modulate the systemic clearance of paclitaxel in patients with cancer to a similar extent. This is in agreement with the evidence of similarity of micelle formation demonstrated for Paxene and Taxol in the *in vitro* studies, therefore it is now demonstrated that micellar formation is unaffected by the presence of citric acid in Paxene. Oxidation is unlikely to occur under the conditions present in Paxene vials. Therefore the equivalence of both Paxene and Taxol formulations is demonstrated. It is scientifically valid to use Taxol clinical data to support the new indications for Paxene.

On the basis of the original Taxol data submitted, paclitaxel at 175 mg/m² in both studies produced higher response rates (29% vs, 22% of mitomycin, p = 0.11 in study 048; 17% vs. 6%, p = 0.14) in study 047. Paclitaxel, given at 175 mg/m², was able to significantly delay tumour progression in both trials (medians of 4.2 vs. 3.0 months, p = 0.027 in study 048; 3.5 vs. 1.6 months, p = 0.026 in study 047). Resistance to prior anthracycline-containing chemotherapy and also resistance to mitomycin did not adversely influence time to progression.

Results of a pivotal, prospectively randomized trial (CA139-022 or GOG-111) which compared Taxol and cisplatin in combination versus the standard regimen of cyclophosphamide and cisplatin in combination in 410 patients with previously untreated, suboptimally debulked FIGO stage III and FIGO stage IV patients with carcinoma of the ovary, supported the claimed indication in MOC. In addition, the published results of 20 other non-randomized trials, involving a total of 498 patients were

presented in a separate report. In these trials paclitaxel was administered as a single agent or, in most cases, in combination, with other drugs (always including a platinum compound).
In addition, Onxol (identical to Paxene) has been in clinical use in the USA since October 2000 in the claimed indications.

Therapy with paclitaxel was well tolerated by the majority of patients. The most common and most important haematological side effects of Paclitaxel were leucopenia and neutropenia. A single case of significant hypersensitivity reaction to Paclitaxel, resulting in treatment discontinuation, occurred in the pivotal studies. The most common and most important non-haematological side effect of Paclitaxel was peripheral neuropathy. Arthralgia and myalgia were also frequently seen in patients receiving paclitaxel. Gastrointestinal side effects (emesis, diarrhoea and mucositis) were very rarely severe. Abnormalities of liver and renal function were unusual and rarely severe. Alopecia was almost universal.

The recommended posology of Paxene in metastatic breast and ovarian cancer is 175mg/m2 via 3-hour infusion every 3 weeks.
Furthermore, it was discussed at the CPMP that another treatment approach in MOC would be to combine Taxol with a platinum drug in first line therapy. Whilst within the European Union the most common first line regimen is a platinum-based combination with paclitaxel there is still a role for non-paclitraxel containing regimens. The lack of preclinical and clinical cross-resistence between Taxol and platinum drugs makes the use of the compound feasible and appealing in previously untreated patients.

3. 5. Overall conclusion and benefit / risk assessment

All the evidence of the *in vitro* studies on Paxene and Taxol including the *in vitro* binding study in human plasma demonstrate that the difference in formulation between the two products does not affect micelle formation/behaviour *in vitro/in vivo*. Clinical data provided on paclitaxel (both from Paxene and Taxol) support the new indications. Therefore, the benefit/ risk of paclitaxel in the indications:

- in the treatment of metastatic breast cancer in patients who have failed or are not candidates for standard anthracycline therapy.
- in the treatment of metastatic ovarian cancer after failure of platinum-containing combination therapy without taxanes.

is favourable.